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# Targeted Nutritional Intervention (TNI) in the Treatment of Children and Adults with Down Syndrome

**Principles behind its use, treatment protocols, and an expanded bibliography.**

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## Introduction and Background

You may have been approached by one of your patients to discuss the issue of Targeted Nutritional Intervention and the use of Piracetam in Down syndrome. You may have, in most cases, drawn a blank or have self-referred back to the era of mega-vitamin therapy and drawn an immediate negative reaction. What is all of this and does it have any grounding in medical science or is it nothing but snake oil?

First of all, it isn't snake oil. The TNI formulation, **NuTriVene-D**, was designed originally by Dixie Lawrence Tafoya. All subsequent modifications were based on journal articles or research and reviewed and approved by the SAC (Scientific Advisory Committee) of Trisomy 21 Research Foundation, Inc. (TRI). Dixie Tafoya first developed this formula based on the work of Henry Turkel, M.D. carried out from the 1940s to the 1970s in which he used a formulation based on some educated guesses. These guesses were made without benefit of formal knowledge of the biochemistry or genetics of Trisomy 21. In fact, when Dr. Turkel first developed his formula, the correct number of human chromosomes was not known nor was it known that Down syndrome was produced by an extra chromosome 21. Today, the ongoing Genome Project in association with improved metabolic assaying techniques has afforded us a better view of the genetics and biochemistry of chromosome 21 in order to make more accurate estimations of what supplementation may help in the

treatment of Trisomy 21.

## Gene Overexpression in Trisomy 21

Most recent gene mapping has sequence all of the genes on chromosome 21 This doesn't mean that they are all known, that process will take more time. But within a few years we should know all of the genes and their protein products. Already several gene families of developmental genes have been found. Some of these because they are turned on only prenatally cannot be influenced but some of them may be amenable to either metabolic or gene therapy in the future. This is exciting new work and has the potential for many new therapies but in the meantime what can be done?

Arguments have been made both pro and con for treating Trisomy 21 as a disease. It is unreasonable to expect that the genes that are present on the additional chromosome 21 are non-functional. In fact, gene dosage studies have shown for many years that many of the genes on 21 are quite functional and producing 40-50% increases of their gene products. Two of these, zinc/copper superoxide dismutase and cystathionine beta synthase are major sources of concern in Trisomy 21. Obviously genes that are developmental in nature such as DYRK and are only turned on in fetal life cannot be affected by any therapy that is begun postnatally but sufficient genes are active to cause a mix of biochemical problems in Trisomy 21.

Is there evidence of metabolic abnormalities in DS? Yes, numerous studies (see Bibliography below) have demonstrated biochemical abnormalities in DS. The first to find these was Jerome LeJeune, who is the physician who first discovered Trisomy 21 as the basis of Down syndrome. LeJeune found that single carbon chains were handled abnormally by people with Down syndrome. This, we now know, is caused by disruptions in the S-Adenosylmethionine cycle or SAM cycle mediated by the enzyme cystathionine beta synthase which is on chromosome 21. The result of these abnormalities is an increased cysteine pool, loss of homocysteine and and decreased methyl groups available for DNA methylation and other biomethylations. Secondary to this is a disruption of folic **acid** metabolism caused by trapping of folate as 5-methyltetrahydrofolate. LeJeune later demonstrated abnormalities in purine synthesis that produces high levels of uric **acid**, presumably caused by the gene GART (first 3 steps in purine synthesis) which is also triplicated.

The zinc/copper enzyme Super Oxide Dismutase (SOD) is well known to be over-functioning in Trisomy 21. It normally is the first step in metabolic conversion of superoxide. Superoxide is a free radical that may cause problems to both the cell membrane and the cell nucleus. SOD produces hydrogen peroxide which two other (not on chromosome 21) gene products, catalase and glutathione peroxidase, convert to nontoxic products. Neither catalase nor glutathione peroxidase are sufficiently upregulated to handle the excess hydrogen peroxide. Hydrogen peroxide is a potent oxidizer which on the cell surface produces lipid peroxidation and compromises the cell membrane, particularly in the presence of excess iron (Fenton reaction). At the organelle and nuclear level, hydrogen peroxide causes damage and stimulates apoptosis

("programmed" death) of the cell. In a study by de Haan et al in Human Molecular Genetics (5:283-292, 1996), it was found that the ratio of SOD to glutathione peroxidase led to increased hydrogen peroxide in the cells and cellular senescence. In a study from Nature (1995), Busciglio and Yankner demonstrated that fetal neuronal cells from non-DS and DS fetuses grew differently. The non-DS cells grew in culture in an orderly fashion but the DS cells grew for only 72 hours and began dying. When a second DS culture was incubated with powerful antioxidants these cells began growing normally. While not direct evidence of the role of reactive oxygen species in the production of symptomotology of DS it certainly provides useful information and a starting place for future studies. This is the logic behind using additional antioxidants in DS.

A recent paper by G. Lubec (2002) J. Neurol. 249: 1347-1356 proposes that molecular evidence of the role of reactive oxygen species and apoptosis of brain cells exists. This evidence is strong and points to antioxident treatment as a means of preventing future damage.

**Immune Dysfunction**
Numerous studies have documented immune dysfunction in Down syndrome including decreased IGA, low white cell counts, and low levels of T-cells. These deficits probably lead to the increased incidence of upper respiratory, ear, and gastrointestinal infection rate in Down syndrome most evident in children but even present in adults. The immune dysfunction seems to be related to zinc depletion but also may be an indirect result of the effects of hydrogen peroxide on immune cells. TNI seems to directly impact this parameter and significant improvement in the incidence of infections is one of the primary effects of TNI.

**Growth**
It has always been assumed that children and adults with Down syndrome will be short. This seems to be a case of self-fulfilling prophecy. Children who are supplemented throughout their lives show a significant increase in growth velocity. In addition, many studies demonstrate an increased incidence of growth hormone deficiency in this population. Looking for and treating growth hormone deficiency may also go towards increasing height in this population. In fact, endocrine dysfunction is not uncommon in Down syndrome. Certainly the connection with hypothyroidism as well as infertility in males with Down syndrome is well known.

**Lipid Handling**
Numerous studies have shown poor lipid metabolism in Down syndrome. Omega 3 and 6 fatty acids (ALA, AA) are decreased. Cholesterol is often increased without a concomitant increase in cardiovascular risk. Apolipoproteins E is abnormal and may contribute to the increased Alzheimer risk in Down syndrome. While DHA (docosohexaenoic **acid**) is not specifically decreased in Down syndrome it is normally low in the diets of nonbreast-fed and American-diet breast-fed infants and children. There is good data to show improvements in brain and retinal development in children supplemented with DHA. DHA has been added to infant formulas in Europe and is currently under consideration for a similar use in the US.

**Alzheimer Disease**

The risk for the development of Alzheimer disease in Down syndrome has been estimated as high as 40%. While these figures are hard to demonstrate, the risk is definitely both increased and also at an earlier age of onset. This does not necessarily translate into clinical symptoms. Alzheimer disease risk in Down syndrome is not related to any one factor but a host of factors including a gene for Alzheimer disease on chromosome 21, lipid handling abnormalities, increased hydrogen peroxide damage to the cells, endocrine abnormalities and reduced acetylcholine receptors in the brain. Current estimates are that over 50% of adults with Down syndrome will develop MRI evidence of Alzheimer disease by age 45.

## General Principles of TNI

TNI is not a cure for Down syndrome. It is a treatment plan that provides additional nutrients and micro nutrients to promote:

- Growth
- Improved health status
- Improved immune function
- Cognitive enhancement
- Prevention or amelioration of long term degeneration and disability.

Does it work? I have been observing patients for the last 7 years who were on this protocol as well as patients not on this protocol. A cohort study has been assembled consisting of 200 patients ranging from 1 month to 4 years of age, and a control group (all on multivitamins) has been followed consisting of 200 patients, ranging from 1 month to 4 years of age. Comparable figures for the two groups were noted for the incidence of congenital heart disease, cardiac surgery, hypothyroidism, day care or school attendance, breast feeding, sex, and race. These observations are subject to the bias that they were not blinded for investigator, patients or parents but still have validity.

Compared to multivitamin controls, the TNI group showed statistically significant differences (improvements) in:

- Growth ($p = 0.02$); in the TNI group, growth went from a mean of the 4th%tile to a mean of the 15th%tile on normal growth charts.
- Decreased upper respiratory infections ($p=.03$).
- Decreased ear infections (.005) and PE tubes (.065). (acutal increase in tubes)
- Decreased gastroenteritis, including repeat incidents or prolonged incidents ($p=.001$).
- IGA levels and white counts were increased ($p=.001$).
- Developmental parameters showed improvement in expressive language($p=0$), gross motor($p=.01$, fine motor($p=.001$), and receptive language($p=.009$).

**Piracetam**

Piracetam, one of a growing group of drugs known as nootropics (which means acting on the mind) is an important part of the TNI protocol. This drug has been used extensively in Europe and Russia originally for the treatment of Alzheimer disease but eventually in the late 1970s in Spain, Italy and Germany for the treatment of Down syndrome. A double-blind study published in 2001 by Lobough et al was a small study with serious methodological flaws. George Capone, M.D. at Johns Hopkins Kennedy Krieger Institute is doing ongoing research into the use of Piracetam. The only known study to date in Down syndrome was an unblinded study from Spain in 1978 that showed improvement in academic performance while taking Piracetam. No serious side-effects were seen and no serious side effects are reported in the very extensive literature that exists for Piracetam. In fact, the LD-50 for Piracetam in laboratory animals requires an IV dose of 8-10 gms/kg, and no oral LD-50 has been reported. The side-effects seen may include headache, gastrointestinal disturbance, fine papular rashes that are transient, and occasionally hyperactivity in children who already show some tendency towards hyperactivity.

Its action in Down syndrome is two-fold. One aspect is the return of membrane fluidity to cell membranes that have undergone lipid peroxidation. Lipid peroxidation is known to be significantly higher in Down syndrome and Alzheimer disease. This lack of fluidity tends to decrease signal intensity in neurons and actually decreases ion flow in and out of cells and thus decreases signal propagation as well. A second effect is the increase in acetylcholine receptors. Acetylcholine receptors have been shown to be decreased in both Down syndrome and Alzheimer disease. Piracetam has been shown by experimental studies to be most active in the corpus callosum of the brain. While no study has shown corpus callosum deficits in the brain of persons with Down syndrome it is an area that is susceptible to lipid peroxidation as is the basal ganglia and hippocampus. Piracetam seems to have its greatest effect in speech production and visual motor coordination/learning.

Piracetam may be prescribed under the Orphan Drug act. It is approved for use in progressive myoclonic epilepsy but to date not for Down syndrome. This, however, is not unusual for Pediatric drugs most of which have never been double-blind tested in children and most of which do not have Pediatric indications. Most pharmacies do not carry it but compounding pharmacies are allowed to make it from base ingredients. It can also be purchased from England or Mexico.

In addition, newer forms of Piracetam such as Pramacetam are coming on the market and may show more efficacy than Piracetam. Alzheimer medications such as Aricept (Donapezil) and Exelon (Rivastigmine) are currently or have been studied with promising results in cognitive improvement and behavior in the preteen, adolescent, and adult groups.

**The Nutrivene D Formula**

*(Disclaimer: Neither I nor any member of the Scientific Advisory Committee of Trisomy 21 Research Foundation, Inc. has, to my knowledge, any financial*

*interest in International Nutrition or any of the products listed below.)*

7 grams will supply the following level of nutrients (As a reference, note that 1 teaspoon = 5 grams):

***Fat-Soluble Vitamins***

Vitamin A (as Beta Carotene, FCC).....3000 IU
Vitamin A (as Palmitate, USP-FCC).....5000 IU
Vitamin D3 (as Cholecalciferol, USP-FCC)..... 200 IU
Vitamin E (as Succinate, USP-FCC)..... 400 IU

***Water-Soluble Vitamins and Related Ingredients***

Biotin (FCC)..... 0.2 mg
Folic Acid (USP-FCC)..... 0.4 mg
Folinic Acid (USP-FCC)..... 0.4 mg
Niacinamide (USP-FCC)..... 125 mg
Pantothenic Acid (as D-Calcium Pantothenate, USP-FCC)... 45 mg
Vitamin B1 (as Thiamin HC1, USP-FCC)..... 45 mg
Vitamin B12 (as Cyanocobalamin, USP)..... 90 mcg
Vitamin B2 (as Riboflavin, USP-FCC)..... 45 mg
Vitamin B6 (as Pyridoxine HC1, USP-FCC)..... 35 mg
Vitamin C (as Sodium Ascorbate, USP-FCC).....1000 mg
Coenzyme Q10..... 30 mg
Inositol (FCC)..... 75 mg
PABA (USP)..... 75 mg
Alpha Lipoic Acid.....45 mg

***Minerals***

Calcium (as Calcium Citrate, FCC)..... 100 mg
Chromium (as Chromium Chloride)..... 75 mcg
Iodine (as Potassium Iodide, USP-FCC)..... 7 mcg
Magnesium (as Magnesium Oxide, USP)..... 150 mg
Manganese (as Manganese Gluconate, USP)..... 1.5 mg
Molybdemun (as Sodium Molybdate)..... 75 mcg
Potassium (as Potassium Chloride, USP-FCC)..... 15 mg
Selenium (as Sodium Selenate)..... 90 mcg
Zinc (as Optizinc)..... 20 mg

***Amino Acids and Related Substances***

L-Citrulline..... 70 mg
L-Glutathione..... 150 mg
L-Histidine (FCC)..... 25 mg
alpha-Ketoglutaric Acid (FCC)..... 500 mg
L-Methionine (USP-FCC)..... 50 mg
L-Ornithine..... 100 mg
L-Proline (USP-FCC)..... 100 mg
L-Serine (USP-FCC)..... 150 mg
L-Tryptophan (FCC)..... 50 mg
L-Tyrosine (FCC)..... 100 mg
Betaine Hydrochloride..... 500 mg

Taurine..... 200 mg

***Miscellaneous***
Choline Bitartrate (FCC)..... 800 mg
Acetyl-L-Carnitine..... 45 mg
Bioflavonoids..... 150 mg
Bromelain (as 80 GDU or 50 MCU)..... 5 mg
Papain (as 16,000 FCC PU/mg)..... 5 mg

***NightTime Formula Ingredients***
Two capsules supply:
Vitamin B6.....5 mg
L-Ornithine.....300 mg
L-Tryptophan.....250 mg

***Daily Enzyme Formula Ingredients***
Three capsules supply:
Alpha-Amylase.....25 mg
Cellulase.....1 mg
Lactase .....1 mg
Lipase.....25 mg

**Nutrivene-D** can be obtained from International Nutrition, Inc., by calling 1-800-899-3413. Dosage is by weight. Person over 16 years of age should request the adult formula. The package comes with 3 bottles: Daily formula, Enzyme capsules and Night-time formula. You can mix up the first two with the piracetam in the morning and give the 3 daily doses that way. The enzyme formula is the one part that can cause problems. If diarrhea occurs stop enzyme and restart with smallest amount you can give and work up to prescribed dose. If diarrhea restarts go back to last dosage without diarrhea. Do not give night-time formula less than 1 hour from bed time. Do night give night time formula closer than 2 hours from last daily supplement. If reflux develops stop the daily enzyme and call International Nutrition.

1. Why do I use **NuTriVene-D** and not other supplements for my patients? The Scientific Advisory Committee of Trisomy 21 Research Foundation, Inc. controls what goes into the formulation. Nothing can be added or subtracted without its approval. It is produced in an FDA-inspected facility under infant formula guidelines and good manufacturing practice (GMP) guidelines.

2. Piracetam is given at 75 mg/kg body weight/day. Dosage will need to be increased every 10 lb. of weight. The Piracetam prescription can be faxed to Hazle Drugs in Hazleton, Pennsylvania. They will call you to activate the prescription. The voice phone number for Hazle Drugs is 1-800-439-2026 (ask for Bill Spears, Jr.). Prescriptions can also be faxed to International Nutrition at 410-902-1767.

3. Efamol or Evening Primrose Oil should be given to augment essential fatty acids. It is available from International Nutrition at 1-800-899-3413.

The dosage is 2 capsules per day for children under the age of 5 or 4 capsules per day for children age 5 and older. Split them up during the day. This comes in a liquid form as well.

4. DHA daily as Neuromins brand from International Nutrition. Open with pin and squeeze out. The dosage 1 capsule per day up to 5 years then 2 capsules per day. DHA now comes a chewable form as well.

5. All children with Down syndrome should be given the following immunizations:
    - Influenza vaccine yearly after one year of age.
    - Acellular Pertussis(Whooping cough) with the DTP will now be listed as DTaP. Give HIB separately not conjugated.
    - Varivax(Chickenpox) vaccine between 1 and 2 years of age.
    - Prevnar in all children. See new Redbook recommendations.
    - All polio vaccine should be IPV (old Salk variety) and not OPV.
    - Measles, mumps, and rubella given by itself.

6. Laboratory Tests:
    - CBC every 6 months until 6 years of age. (Looking for leukemia)
    - T3, T4 and TSH every year for life. (Thyroid testing)
    - Atlantoaxial X-rays at 2 years of age especially in active children. (Looking for atlantoaxial dislocation)
    - Metabolic Testing:
        - If working through a local lab only: Obtain serum levels of Vitamin A, folic **acid**, a lipid profile, iron, ferritin, zinc, selenium, and homocysteine, IgA, endomyseal antibody.

7. Medications to avoid include sulfa-containing antibiotics (Pediazole, Gantrisin, Septra, Bactrim). Sulfa drugs can further deplete zinc in zinc-depleted children. If sulfa drugs must be used, then an additional 10 mg a day of zinc should be supplemented while the child is taking the sulfa drugs. Do not give the child additional vitamins without first checking with us. Do not give the child additional iron unless the child has proven iron deficiency anemia. Iron increases the Fenton reaction and thus lipid peroxidation. Additionally, excess iron is often stored in the brain and may contribute to long-term CNS dysfunction.

8. Please keep a detailed illness log and a development log in all.

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